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Failure to Respond after Reinstatement of Antidepressant Medication: A Systematic Review

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Keywords

Antidepressants · Depressive disorder · Anxiety disorder · Obsessive-compulsive disorder · Posttraumatic stress disorder · Reinstatement · Systematic literature review · Failure to respond · Tachyphylaxis

Abstract

Background: Following remission of an anxiety disorder or a depressive disorder, antidepressants are frequently discontinued and in the case of symptom occurrence reinstated. Reinstatement of antidepressants seems less effective in some patients, but an overview is lacking. This systematic review aimed to provide insight into the magnitude and risk factors of response failure after reinstatement of antidepressants in patients with anxiety disorders, depressive disorders, obsessive-compulsive disorder (OCD), or posttraumatic stress disorder (PTSD). ***Method:*** PubMed, Embase, and trial registers were systematically searched for studies in which patients: (1) had an anxiety disorder, a depressive disorder, OCD, or PTSD and (2) experienced failure to respond after reinstatement of a previously effective antidepressant. ***Results:*** Ten studies reported failure to respond following antidepressant reinstatement. The phenomenon was observed in 16.5% of patients with a depressive disorder, OCD, and social phobia and occurred in all common classes of antidepressants. The range of response failure was broad, varying between 3.8 and 42.9% across studies. No risk factors for failure to respond were investigated. The overall study quality was limited. ***Conclusion:*** Research investigating response failure is scarce and the study quality limited. Response failure occurred in a substantial minority of patients. Contributors to the relevance of this phenomenon are the prevalence of the investigated disorders, the number of patients being treated with antidepressants, and the occurrence of response failure for all common classes of antidepressants. This systematic review highlights the need for studies systematically investigating this phenomenon and associated risk factors.

R.C.B. and R.C.W. contributed equally to this work.

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Introduction

Antidepressant medication is used to treat up to two thirds of patients with anxiety and depressive disorders [1], with an increasing number of patients using antidepressants long term [2]. It is frequently assumed that the response to antidepressants in patients remains stable over time, but there are observations that this is not the case.

Firstly, during continuous treatment with an antidepressant the effect of the antidepressant may decrease [3–7]. One study suggests that this "poop out" phenomenon is more prominent in selective serotonin reuptake inhibitors than in selective serotonin and noradrenalin reuptake inhibitors and tricyclic antidepressants [6].

Secondly, the response to antidepressants may decrease with repeated exposure [8, 9]. Two clinical trials reported that in patients with major depressive disorder (MDD) or bipolar II disorder the number of previous exposures to antidepressants was negatively related to the treatment response in a following trial with antidepressants [8, 9]. Indications for this phenomenon were also found in the STAR*D trial, a naturalistic study investigating the response to antidepressants in successive treatment steps [10]. It was found that the response to the first treatment step was lower in patients who had received previous treatment for the current episode compared to patients who had not received treatment for the current episode.

Thirdly, response failure can occur when an initially effective antidepressant is discontinued following symptom remission and reinstated after the occurrence of symptoms. This situation frequently occurs in daily clinical practice because: (1) anxiety and depressive disorders are highly prevalent [11], (2) up to two thirds of patients receive antidepressants [1], (3) many patients achieve remission while on antidepressant medication [12–22], (4) treatment guidelines advise discontinuation after a period of sustained remission [12, 14–23], (5) and 36 or 41% of patients with, respectively, anxiety disorders or depressive disorders experience symptoms following antidepressant discontinuation [24, 25]. These are often labelled as relapse, but according to Chouinard and Chouinard [26] these symptoms can also be explained as newly occurring symptoms caused by the withdrawal of antidepressants. For these patients the effectiveness of antidepressants after reinstatement is of utmost importance. Unfortunately, there are indications that reinstatement of the same antidepressant after the occurrence of symptoms does not necessarily yield an effect similar to that in the period prior to drug discontinuation. Two case studies reported that with reinstatement of the same previously effective antidepressant the subsequent response was absent [27, 28].

Little is known, however, about this third type of response failure. Although 2 literature reviews have been conducted [29, 30], no systematic review of failure to respond to antidepressants after reinstatement of the same medicament has previously been published. Therefore, we systematically reviewed the available empirical literature focusing on failure to respond again to the same antidepressants following reinstatement due to the occurrence of symptoms in patients with depressive disorder, anxiety disorders, obsessive-compulsive disorder (OCD), or posttraumatic stress disorder (PTSD).

Method

Literature Search

PubMed and Embase were searched (from inception to July 2017) for empirical studies including adult (age ≥18 years) patients with an anxiety disorder, a depressive disorder, OCD, or PTSD who had an initial response to an antidepressant but after discontinuation and later reinstatement of the same antidepressant experienced an ineffective or less effective response. Additionally, the reference lists of the included articles were screened and several trial registers were searched (i.e., Cochrane Library, Current Controlled Trials, Clinical Trials, The Netherlands Trial Register, and NHS Centre for reviews and dissemination). Included were manuscripts containing original research data and English language publications only. Case studies and case series were excluded.

The used search string included terms referring to reinstatement of treatment, anxiety disorders, depressive disorders, OCD, and PTSD and antidepressant medications (see online suppl. 1 for the complete search strategy; for all online suppl. material, see www.karger.com/doi/10.1159/000491550). The search was conducted by an experienced librarian, R.C.B., and R.C.W. In accordance with PRISMA guidelines [31, 32], the studies were selected by 2 independent reviewers (R.C.B. and R.C.W.). Firstly, studies were assessed for eligibility based on their title and abstract. Secondly, both reviewers assessed the full text of the selected articles. In case of disagreement, consensus was reached by referral to the text and discussion within the project group (R.C.B., R.C.W., N.M.B., and A.J.L.M.B.).

Data Extraction and Analysis

Data extraction forms were generated based on the Cochrane data collection form for clinical trials [33]. The following information was extracted: study details (year of publication, country of study, single- or multi-center study), participant details (number of participants, inclusion and exclusion criteria, age, gender, type of disorder, comorbidity and number of previous episodes, number of participants with and without failure to respond), medication details (antidepressant type, class, dose, and frequency; discontinuation mode [abrupt vs. tapered], comedication), methodological details (study design, study duration, time points of

measurements, version of diagnostic tool, definitions of response, remission, and occurrence), information about the course of response failure, and risk factors. R.C.B. and R.C.W. extracted data from half of the articles and then checked the other half of the data. Disagreements were solved by referral to the data.

Quality Assessment and Publication Bias

The quality of the studies was assessed using the Cochrane Collaboration tool [34]. Assessed aspects were related to the demographics and clinical characteristics of the population at reinstatement, the treatment with antidepressants with an effect and the treatment with antidepressants with response failure, and potential confounders. R.C.B. did the initial scoring of the studies, and this was double-checked by R.C.W. In case of disagreement, consensus was reached through discussion.

Results

Literature Search

The search of PubMed and Embase resulted in 10,850 unique records; of these, 10,700 were excluded based on their title and abstract, resulting in 150 records for full-text screening (online suppl. 2). We were unable to acquire a full-text copy of 4 articles. Of the remaining 146 records, 8 articles could be included [35–42]. The search of the reference lists of the included articles resulted in the additional inclusion of 2 articles [43, 44]. No additional records were included based on the search of trial registers. This systematic review thus contains 10 studies.

Study Characteristics

Online supplement 3 provides an overview of the characteristics of the 10 included studies. The studies were published between 1989 and 2006 and consisted of 1 retrospective chart review [42] and 9 prospective studies with reinstatement after the occurrence of symptoms [35–41, 43, 44]. Most prospective studies [36–41, 43, 44] were not placebo controlled. The sample sizes in the reinstatement phase ranged from 11 to 81 participants. Response and/or remission at reinstatement was defined in varying ways across studies (online suppl. 4). Failure to respond has been reported in patients diagnosed with MDD and/or dysthymia [35–38, 41–44], OCD [39], and social phobia [40]. We did not find studies regarding other anxiety disorders (e.g., generalized anxiety disorder, panic disorder, specific phobia) or regarding PTSD.

From online supplement 3 it appears that failure to respond was reported in 16.5% of patients restarting an antidepressant (394 exposures leading to 65 patients with response failure). The range across studies reporting failure to respond was broad, ranging from 3.8 to 42.9%. In 1 study the patients did not have any previous episodes [37], while in 2 studies the patients had had at least 1 previous episode prior to study baseline [41, 42], and in 1 study the patients had had at least 3 previous episodes [43]. The other 6 studies did not report whether the patients had experienced prior episodes [35, 36, 38–40, 44]. Failure to respond following reinstatement has been observed for monoamine oxidase inhibitors [37, 40], tricyclic antidepressants [37–39, 41–44], selective serotonin reuptake inhibitors [35, 39], and selective serotonin and noradrenalin reuptake inhibitors [36] and thus in all common classes of antidepressants. Apart from the study of Flint and Rifat [37], no studies reported on comedication (online suppl. 3).

Depressive Disorders

Following open-label treatment, 6 studies prospectively followed participants diagnosed with MDD [35–37, 41, 43, 44] and 1 study followed patients with pure dysthymia or dysthymia with MDD [38] (online suppl. 3). These studies included 21–501 patients with response to antidepressant treatment of the index disorder, and 11–58 of those patients received retreatment following the occurrence of symptoms. Response failure occurred in patients treated with desipramine ($n = 2$ [8.3%], 200 mg/day [44], and $n = 1$ [8.3%], 75–300 mg/day, with plasma levels ranging from 150 to 300 ng/mL [38]), imipramine ($n = 7$ [18.9%], median dose 200 mg/day, with a median plasma level of 300 ng/mL [43]), nortriptyline ($n = 3$ [10.0%], mean dose 80.4 mg/day, plasma level 95.1 ng/mL [41]), fluoxetine ($n = 6$ [10.9%], 20 mg/day [35]), and duloxetine ($n = 15$ [26.3%], 60 mg/day [36]). One study [37] reported response failure after reinstatement of nortriptyline or phenelzine corresponding to what patients had previously received ($n = 1$ [9.1%]), but it did not specify the dosage or the antidepressant. In 3 studies patients simultaneously received psychological treatment and antidepressant treatment for their symptoms [41, 43, 44]. Following the occurrence of symptoms, psychological treatment and antidepressant treatment were both reinstated in 2 of the 3 studies [41, 43].

In addition to these 7 prospective follow-up studies, 1 study consisted of a retrospective chart review [42] (online suppl. 3). Based on the medical records of patients with MDD it was found that, of the 35 patients who received the same antidepressant medication and dose as in the previous episode, 15 (42.9%) no longer responded [42].

Anxiety Disorders

One study [40] investigated the long-term treatment outcomes of moclobemide (mean dose 730 mg/day) for social phobia (online suppl. 3). In that prospective study, patients were treated for 2 years followed by a no-treatment period of at least 1 month. When a patient experienced occurrence of symptoms, treatment was reinstated for another 2 years, again followed by a no-treatment period of at least 1 month. Of the patients ($n = 51$) who were retreated with moclobemide for 9 months, 2 (3.8%) no longer responded.

Obsessive-Compulsive Disorder

One study reported on failure to respond after reinstatement of antidepressants in OCD [39], using a prospective design to assess whether patients with OCD had a similarly effective response after the same drug was reinstated following the occurrence of symptoms (online suppl. 3). They found that out of the 81 patients who experienced occurrence of symptoms and were retreated with clomipramine (150 mg/day), fluoxetine (40 mg/day), fluvoxamine (300 mg/day), or paroxetine (40 mg/day), 13 (16.0%) had an ineffective or less effective response when retreated with the same drug at the same dose compared to the initial trial. No differences were observed for the different drugs [39].

Risk Factors

None of the included studies investigated risk factors for response failure to antidepressant medication.

Quality Assessment and Publication Bias

In all of the studies information was missing to some extent, though the amount of missing information varied between studies (online suppl. 5). Demographic information was missing in 3 studies [37, 39, 42]. One study only reported information about the baseline population [40] but not specifically about the group in which antidepressants were reinstated. In most studies it was difficult to determine whether antidepressant treatment and reinstatement were adequately administered. Information was missing about which specific antidepressant had been used in treatment [42], for which antidepressant failure to respond had occurred [37, 42], the dose and frequency of antidepressant treatment and reinstatement [37, 42], the duration of the treatment [37, 41–44], the duration of reinstatement [37, 38, 41–44], and the plasma levels of tricyclic antidepressants during treatment and/or reinstatement [37–39, 42, 44].

Several types of bias may also be present (online suppl. 5). Reporting bias could have occurred as most studies are subgroup analyses of a larger study [35–39, 44–46] and it is not reported how these subsamples corresponded to the overall sample in terms of numbers and/or characteristics. In 3 studies it was also not clear which participants were included in the statistical analyses of the reinstatement phase [36, 40, 44], which could have resulted in either underestimation or overestimation of the number of patients with response failure. Bias could also have been introduced due to inadequate blinding of patients, practitioners, and/or outcome assessors in most studies and thus outcome expectancies could have influenced the results. This can result in overestimation of the effect of treatment [47, 48], and as thus reinstatement of antidepressants may have been considered more effective in patients than it actually was, thereby underestimating the proportion of response failure. Moreover, the study outcomes could have been affected by the allowance of comedication [37] and psychotherapy [41, 43, 44] or by not excluding comorbid disorders [40, 41].

Discussion

The aim of this systematic review was to provide an overview of empirical literature reporting failure to respond after reinstatement of antidepressant medication that was previously effective in patients with depressive disorder, anxiety disorder, OCD, or PTSD. The results showed that 16.5% (range 3.8–42.9%) of the patients experience failure to respond and this occurred in all classes of antidepressants. This phenomenon is thereby clinically relevant.

Our review suggests that a stable response to antidepressants after reinstatement cannot be assumed in all patients. Given that a decrease in the effect of antidepressants has also been reported during continuous antidepressant use [3–7], with repeated exposures [8–10], and in patients with recurrent episodes [49], it is possible that these different types of response failures reflect a broader phenomenon. Therefore, it is important to investigate which mechanisms underlie response failure to antidepressants and whether the core mechanisms are similar for all of the aforementioned varieties of response failure.

The included studies proposed some possible pharmacodynamic mechanisms. Three studies suggested that patients who no longer responded were initially placebo responders and thus never had a "true" drug response [35, 39, 44]. This hypothesis was, however, disregarded by

Maina et al. [39], who considered it unlikely that a placebo response existed for the entire duration of the 6-month treatment phase. An alternative hypothesis, suggested by 2 studies [35, 44], was that patients had developed a "tolerance" to antidepressants over time and therefore did not respond anymore after reinstatement. Since the possible underlying pharmacological mechanisms were not explained by the authors and have not been studied systematically, they remain speculative.

Moreover, response failure could also be the result of progression of the disease [39, 42]. For depressive disorders, it is known that with an increasing number of episodes the likelihood of symptom occurrence also increases [50–53], potentially resulting in a chronic course with a more severe symptomatology [54]. Thus, the effectiveness of the antidepressants may remain unchanged, but the underlying disorder may become more severe and can no longer be effectively treated. It is difficult to determine if this is a relevant factor in the present study because 6 of the 10 included studies did not report the duration of the index disorder or the number of previous episodes. In the studies that reported on duration, there were no clear indications of a relationship between duration or number of previous episodes and failure to respond. One study reported that patients had no previous episodes [37], and 2 other studies reported that patients had at least 1 previous episode [41, 42]. Only 1 study included patients with multiple previous episodes (mean 6.2) [43]. The proportion of response failure across these studies were 9.1 [37], 42.9 [42], 10 [41], and 18.9% [43], respectively. An argument in favor of this disease progression hypothesis is that the proportion of response failure seems to be comparable to occurrence rates during maintenance treatment [24, 25]. However, since there is no direct comparison with maintenance therapy, the studies included in this review cannot substantiate this hypothesis.

Although the underlying mechanisms are still unclear, it is important to consider a possible harmful role of antidepressants in the process of response failure. The oppositional model of tolerance states that it cannot be excluded that antidepressants have a detrimental effect on the course of illness in anxiety disorders and depressive disorders [29, 30]. According to this model, "continued drug treatment may recruit processes that oppose the initial acute effects of a drug and may result in failure to respond" [p. 127 in 29], which may explain response failure following reinstatement of the initial effective antidepressant. The model further states that "continued antidepressant treatment may also propel the illness to a more malignant and treatment-unresponsive course" and that following discontinuation "oppositional processes may operate for some time, resulting in withdrawal symptoms, and increased vulnerability to relapse or resistance when treatment is reinitiated" [29, p. 127]. These potential iatrogenic effects of antidepressants should be further examined, especially because long-term antidepressant use is increasing [2].

Failure to respond could also result from transition of the index disorder to another disorder. In patients with MDD who are resistant to antidepressant treatment, the diagnosis is more frequently changed from MDD to bipolar disorder compared to patients without antidepressant resistance [55]. Transition from MDD to bipolar disorder does not explain why response failure is also observed in OCD and social phobia, and the time span of the included studies is to limited for observation of transition.

In addition to pharmacodynamic mechanisms and disease-related factors, changes in the pharmacokinetics of antidepressant drugs over time may contribute to response failure during subsequent episodes of depression or anxiety. Specifically, an increased drug metabolism in subsequent episodes compared to the index episode can reduce plasma drug concentrations and, as a consequence, drug efficacy. Cytochrome P450 (CYP) induction related to comedication or other factors like smoking could influence drug metabolism and is particularly relevant to antidepressant drugs metabolized by CYP3A4, CYP1A2, CYP2C9, and CYP2C19 [56]. Most of the included antidepressants associated with a failure to respond are primarily metabolized by CYP2D6. Since CYP2D6 is generally accepted to not be inducible [57], pharmacokinetic changes are not expected to contribute substantially to subsequent response failure to antidepressant drugs.

To our knowledge, this is the first review that specifically investigates failure to respond following reinstatement of an antidepressant after successful treatment for the same disorder with a systematic approach. A major strength of this review is that we conducted a broad literature search, checked the reference lists of the included studies, and searched trial registers for relevant studies. Therefore, it is probable that we captured most of the available literature on this topic. The results of this systematic review should, however, be interpreted in the context of the following limitations.

The included studies consist of 9 prospective studies with reinstatement after the occurrence of symptoms and 1 retrospective chart review. These are nonsystematic studies with methodological inconsistencies. Across

studies different definitions for response failure were used, limiting the comparability of the studies. Also, in studies that provided simultaneous antidepressant and psychological treatments, the independent effects of these treatments could not be untangled in either the initial phase or the reinstatement phase. As a result, this could have led to underestimation of the number of nonresponding patients.

Furthermore, none of the included studies reported any risk factors for response failure. Consequently, it remains unknown which patients are potentially at risk and which patients can restart antidepressants in a relatively unproblematic manner following the occurrence of symptoms. Additionally, whether response failure also occurs in more recently introduced antidepressants is unknown, as the most recently published study in this systematic review is from 2006. Moreover, because the included studies were of low to moderate quality and bias may be present, no firm conclusion can be drawn. These limitations highlight the need for up-to-date good-quality research.

In recent years some attention has been paid to response failure [58]. This systematic review shows, however, that the phenomenon is largely understudied and consists of older studies (from 2006 and earlier) and that the majority of studies conducted are of low to moderate quality.

Although a failure to respond only seems to occur in a minority of patients restarting antidepressants (16.5%, range 3.8–42.9%), it is of clinical relevance given the high number of patients taking antidepressants [1], the occurrence of the phenomenon in all common classes of antidepressants, the high prevalence of anxiety disorders, depressive disorders, OCD, and PTSD [11], and the tendency of these disorders to run a chronic course in which the occurrence of symptoms is common [24, 25, 54, 59–67, 68–70].

This systematic review identified the need for high-quality studies investigating the phenomenon of response failure. The European Medicines Agency (EMA) currently requires that medication trials for anxiety disorders, depressive disorders, OCD, and PTSD have a placebo-controlled continuation phase varying between 6 and 12 months of follow-up [71–76]. To increase our understanding of the phenomenon and its etiology and to better advise patients, response failure after reinstatement should be compared to response failure during maintenance therapy. A first recommendation might be that placebo-controlled discontinuation trials also investigate to what extent patients who switch to the placebo-arm and experience occurrence of symptoms respond again to the medication under study. This will result in more systematic research in a larger population, insight into the occurrence of response failure in other disorders or in recently developed medications, and determination of possible risk factors. Additionally, investigation of underlying mechanisms of failure to respond is recommended. When patients at risk for response failure after reinstatement can be identified in the future, personalized treatment advice can be given in order to improve the long-term prognosis of the patients.

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